Meta-Potentiation: Neuro-Astroglial Interactions Supporting Perceptual Consciousness

Alfredo Pereira Jr.* and Fábio Augusto Furlan**

*****Adjunct Professor - Institute of Biosciences - São Paulo State University (UNESP) - 18618-000 - Botucatu-SP - Brasil; e-mail: apj@ibb.unesp.br
** Assistant Professor - Faculty of Medicine and Nursing - University of Marília - e-mail: fabioaugustofurlan@yahoo.com.br

Abstract

Conscious perceptual processing involves the sequential activation of cortical networks at several brain locations, and the onset of oscillatory synchrony affecting the same neuronal population. How do the earlier activated circuits sustain their excitation to synchronize with the later ones? We call such a sustaining process "meta-potentiation", and propose that it depends on neuro-astroglial interactions. In our proposed model, attentional cholinergic and stimulus-related glutamatergic inputs to astroglia elicit the release of astroglial glutamate to bind with neuronal NMDA receptors containing the NR2B subunit. Once calcium channels are open, slow inward currents activate the CaM/CaMKII complex to phosphorylate AMPA receptors in a population of neurons connected with the astrocyte, thus amplifying the local excitatory pattern to participate in a larger synchronized assembly that supports consciousness.

Key-words

Meta-potentiation, Consciousness, Oscillatory Synchrony, Astrocyte, Slow Inward Currents.

1 - Introduction

Two fields of experimental research have contributed to the progress in the scientific study of consciousness: a) neuroimaging combined with the performance of cognitive tasks and linguistic report of conscious states by human subjects (Lloyd, 2002; Kamitami and Tong, 2005; Rees, 2007), and b)

single and multichannel records of brain activity during cognitive tasks (Coull, 1998, Rodriguez et al., 1999).

Several results indicate that the occurrence of conscious processing correlates with the brain hemodynamic response and oscillatory synchrony. This correlation is, of course, too vague to count as an explanation, as they may also be related to unconscious processes (e.g. 3 Hz oscillations in Slow-Wave Sleep).

In this paper, we attempt to move one step forward into the identification of a closer correlate of consciousness, a kind of activity that is present only when conscious processing occurs. Our strategy to find a univocal correlate of consciousness is to search for a kind of brain activity that underlies both hemodynamic responses and oscillatory synchrony, and then to make an analysis of the components of this activity to identify those that satisfy suitable temporal and populational criteria.

Based on the work of Logothetis et al. (2001) and Logothetis and Pfeuffer (2004), we found that the hemodynamic response measured by BOLD fMRI is closely related to Local Field Potentials (LFPs). LFPs are complex phenomena reflecting simultaneous slow synaptic activities of neuronal populations. These activities include excitatory and inhibitory postsynaptic potentials, and several modalities of membrane afterpotentiation. Some – but not all – mechanisms underlying the generation of LFPs probably participate in the generation of the kinds of oscillatory synchrony related with conscious processing. Which are the components of LFPs specifically related to conscious processing?

In order to find an answer to the question, we use two criteria. First, the consciousness-related component(s) should be able to sustain a continuous sequence of excitatory postsynaptic potentials (EPSP) from around 200

milliseconds to 2/3 seconds, to allow conscious processing to occur. Second, the consciousness-related LFP component(s) cannot be restricted to the single neuron, but should affect a large cellular population, in order to elicit oscillatory synchrony (and also to have an impact on the hemodynamic response).

We suggest that *neuro-astroglial interactions* (Antanitus, 1998) provide the link between local and global excitatory patterns. These interactions occur at the glutamatergic tripartite synapse, where the release of presynaptic glutamate - and other mediators - induces calcium waves in astrocytes, leading to the release of astroglial glutamate and the resulting activation of NMDA receptors of the postsynaptic neurons and other neurons connected to the astrocyte.

Such a conjoint activation elicits the formation of a local assembly that propagates the excitation to other parts of the brain, triggering oscillatory synchrony and then the formation of a large-scale functional assembly putatively supporting perceptual consciousness. This phenomenon provides broad afterpotentiation effects in neurons pertaining to the functional assembly, providing the sustaining of excitation in lower-order (sensory) cortical areas while the sequence of activations reach higher-order (associative) cortical areas.

We call this afterpotentiation effect *meta-potentiation*, in order to distinguish it from other modalities of membrane potentiation, as well as from other kinds of afterpotentiation effects. Meta-potentiation is proposed to be a necessary mechanism to make possible the phase-locking of membrane electric oscillations in perceptually activated brain circuits, forming a functional collective.

2 – On the Temporal Dynamics of Consciousness

Available data (Laureys, 2005; Buszáki, 2007) indicate that conscious processing requires the co-activation of a large network of brain systems. In perceptual processes, in order to achieve a global coherent pattern of activation, the brain begins with the formation of distributed LFPs in primary sensory areas. Each sensory neuron (or each small-scale functional assembly in cortical tissue) responds to one aspect of the stimulus (the "receptive field"). The local sum of activity - composing a LFP - is well correlated with hemodynamic changes detected by BOLD fMRI.

As soon as local fields are generated, the brain uses another mechanism to integrate local patterns into a global pattern of activity. This strategy implies that each local field participating in the generation of a conscious episode should be sustained for some time, even after the decay of stimulation. During this period of sustained activity they possibly interact with other local fields, spatially distributed in the brain, to generate the content of a conscious perceptual episode.

The identification of the temporal dynamics of consciousness by means of behavioral events is difficult, since in many cases conscious perception emerges *after* the triggering of a behavioral response. Consciousness can occur 500 ms after the beginning of a behavioral response, according to Libet (1973, 2004).

Reaction times are also relative to the perceptual modalities involved, and proportional to the inter-modal integrative and supplementary cognitive processes necessary to generate the behavioral response to the presented stimulus. They are typically shorter for single-modality signal detection, and progressively longer for multimodal integration and for tasks that require cognitive processing and/or selection of alternatives.

Pöppel and Logothetis (1986) measured reaction times to visual stimuli, and calculated that perceptual processing operates in units of 30 milliseconds. This result is consistent with the role of gamma synchronous oscillations in conscious perception (Poppel et al., 1990). It can also be applied to auditory processing and inter-hemispheric integration required by a sensory-motor task (Pöppel, Schill and von Steinbüchel, 1990).

Based on these results, Pöppel proposed a model of conscious perceptual processing containing two temporal constraints. The basic unit is estimated to be around 30 ms, while conscious episodes composing the "conscious present" can be extended to periods of 2 or 3 seconds (Pöppel, 1994).

Progress in the estimative of the temporal dynamics of conscious perceptual processing came from the measurement of brain events directly correlated to the processing (not to the behavioral response). This strategy is used in the Event-Related Potential (ERP) paradigm. Measurement of the temporal location of brain events correlated with conscious processing evoked by stimulus presentation can be found in ERP studies in human subjects, some of them involving linguistic processing. This method is able to measure electric phenomena temporally correlated with conscious processing. For instance, the ERP P300 and N400 components are related to working memory and/or attention functions that probably involve conscious processing (Knight, 1997; Coull, 1998). The corresponding brain events occur from 300 to 400 ms after stimulus presentation.

There are also other ERP that take longer temporal intervals to occur, but for the purpose of this study we assume 200 ms to be a good estimative about the minimum temporal duration from stimuli presentation to the formation of a conscious percept. This interval is consistent with data from

Rodriguez et al (1999**).** In the process of image (face) recognition, gamma synchronous oscillations occurred at 230 and 800 ms after external stimulation. This second synchronous period refers to a motor response, while the first period correlated well to perceptual conscious processing.

Subtracting from the 230 ms interval the time necessary for sensory transduction to the CNS and generation of unconscious activity at several brain locations, the minimum latency time for conscious processing would be around 200 ms. Therefore, the sustaining of neuronal activity necessary to support conscious processing would range *from 200 ms to 2/3 seconds*. How does the brain achieve this result?

3 - Meta-Potentiation

Earlier attempts to identify a univocal correlate of consciousness focused on axonal spikes. Crick and Koch (1990) proposed that the neuronal correlate of visual consciousness was the phase-locked firing of neurons at 40 Hertz. Later they refined the hypothesis, stating that increased spiking activity at some cortical locations (with emphasis on bursting cells located at cortical layer 5) would be more crucial for visual consciousness (Crick and Koch, 1994).

An increase in firing rates of input neurons is surely important to generate neuronal excitation underlying the hemodynamic response (related to the formation of LFPs) and synchronized oscillations in neuronal populations. It is well known that presynaptic axonal spikes contribute to generate EPSPs by means of releasing excitatory neurotransmitters at the axon terminal to bind with postsynaptic membrane ionotropic receptors. This is a usual pathway by which an increase in presynaptic firing rates becomes the cause of increase in postsynaptic excitation.

Studies on subliminal perception (Murphy and Zajonc, 1993) reveal that the time of presentation of a stimulus is important to determine if it is conscious or unconsciously perceived. A visual stimulus presented for only 5 ms and followed by a mask is not consciously perceived, although it may have unconscious priming effects. This requirement implies that input firing is *necessary* for perceptual consciousness, although not sufficient. According to our previous analysis, temporal sustaining of neuronal activity (from the scale of hundreds of milliseconds to the scale of seconds) and population synchronization elicited by the input signal are required for conscious processing.

Depending on their target, axonal spikes can also cause inhibitory activity and membrane hyperpolarization. Logothetis (2001) showed that the hemodynamic response overlaps with LFPs measured by extracellular electrodes placed in the dendritic network, but not with the activity measured by single-cell electrodes placed at the axon hillock of neurons, or by multiple-unit activity. One of the reasons of such a non-correlation is that membrane hyperpolarization can contribute to the magnitude of the fields and the response, but not to an increase in firing rates of the same neurons. For the sake of simplicity, in the following we will not consider the contribution of hyperpolarization to the activity measured by fMRI.

The LFPs measured by Logothetis were elicited by sustained stimulation (during intervals from 4 to 24 seconds). They depended on the maintenance of high input spike rates at the measured regions. However, in the study of consciousness we are mostly interested in what happens *after* external stimulation ceases and the corresponding presynaptic spike rates decay. What occurs after presynaptic stimulation ends?

There are four possibilities:

a) postsynaptic excitation spontaneously decreases to the baseline;

b) postsynaptic excitation decreases to the baseline or below it, because of an inhibitory action made by other neurons;

c) postsynaptic excitation is sustained, in the same neuronal population or elsewhere, for a task that is independent of conscious processing; and

d) postsynaptic excitation is sustained, in the same neuronal population or elsewhere, *exclusively for* conscious processing.

Considering that conscious processing requires an appropriate temporal dynamics (from 200 ms to 2/3 secs), and considering that it does not always depend on constant stimulation, we assume that *the sustaining of postsynaptic activity* after the decay of presynaptic firing rates, leading to the onset of oscillatory synchrony in a larger neuronal population, could be taken as *a reliable index* of conscious processing.

With this assumption, the investigation should focus on postsynaptic mechanisms that sustain neural excitation beyond 200 ms after the decay of presynaptic stimulation. Since conscious processing is related to the activity of LFPs and oscillatory synchrony, the mechanism implies the involvement of a neuronal population to (putatively) integrate the activity of multiple LFPs distributed along the brain into a unitary conscious episode.

The initially excited neuronal population has the role of triggering an excitatory pattern in a larger population, being able to return to baseline or become hyperpolarized soon after accomplishing this task. The dynamics of excitatory activity that corresponds to conscious processing does not necessarily affect the same neurons from the beginning to the end, but can be temporally distributed in sequentially activated populations.

Therefore, the LFP component that is more closely related to conscious processing is the one that leads to the generation of a global excitatory pattern

affecting a large neuronal population. In order to identify this component, we distinguish three postsynaptic phases:

a) *excitatory postsynaptic response to presynaptic input:* in the glutamatergic synapse, the postsynaptic response lasts up to 150 ms (Haydon and Carmignoto, 2006), and includes the sequential opening of AMPA and NMDA channels, eliciting several processes that increase the spiking activity of the postsynaptic neuron, and may also take part in short-term and/or long-term potentiation (STP/LTP) processes;

b) *afterpotentiation effects:* following the beginning of the primary postsynaptic response, a variety of excitatory processes occur, generating several afterpotentiation effects. These processes include: presynaptic reinforcement by means of retrograde messengers (nitric oxide, arachidonic acid) promoted by activation of NMDARs; backpropagation of potentials in each neuron; excitatory modulation of ionotropic receptors by means of metabotropic receptor G-protein pathways, and the opening of voltage-gated ion channels;

c) *meta-potentiation*: afterpotentiation effects trigger a continuous sequence of events that reach a larger neuronal population exclusively for the task of conscious processing. Considering that conscious processing can extend to periods of 2/3 seconds, and involves sustained excitation of large neuronal populations, the previously mentioned neuronal mechanisms are not sufficient to generate it. We propose that meta-potentiation can be explained by means of *the participation of astrocytes* in tripartite synapses and extrasynaptic transmission.

An important note to the above definition is that the three proposed postsynaptic phases can partially overlap, i.e., they compose a sequential process in which the beginning of one phase necessarily precedes the

beginning of another phase, but the ending of one phase does not have to occur before the beginning of the next phase.

4 - Astroglial Contribution to Meta-Potentiation

Recent results on astroglia research indicate that these cells participate in glutamatergic tripartite synapses (Haydon and Carmignoto, 2006), contributing to the onset of synchrony (Fellin et al., 2004). Considering that consciousness requires the coordination of local and global patterns of activity in the brain (Buszáki, 2007), the above results qualify neuro-astroglial mechanisms to be a link between local and global activity.

In our proposed model (Fig. 1), the excitatory period supporting consciousness begins with presynaptic neuronal Glutamate (Glu) release and binding with postsynaptic AMPA. The opening of this ionotropic receptor triggers several excitatory activities, producing postsynaptic membrane excitation that lasts up to 150 ms after presynaptic stimulation extinction. While this excitation lasts, the presynaptic Glu also binds with NMDA receptors belonging to neighbor astrocytes. Astrocytic NMDA receptors, upon binding with presynaptically released Glu, induce calcium waves that promote the release of astrocytic Glu, which binds with neuronal NMDA containing the NR2B-type subunit.

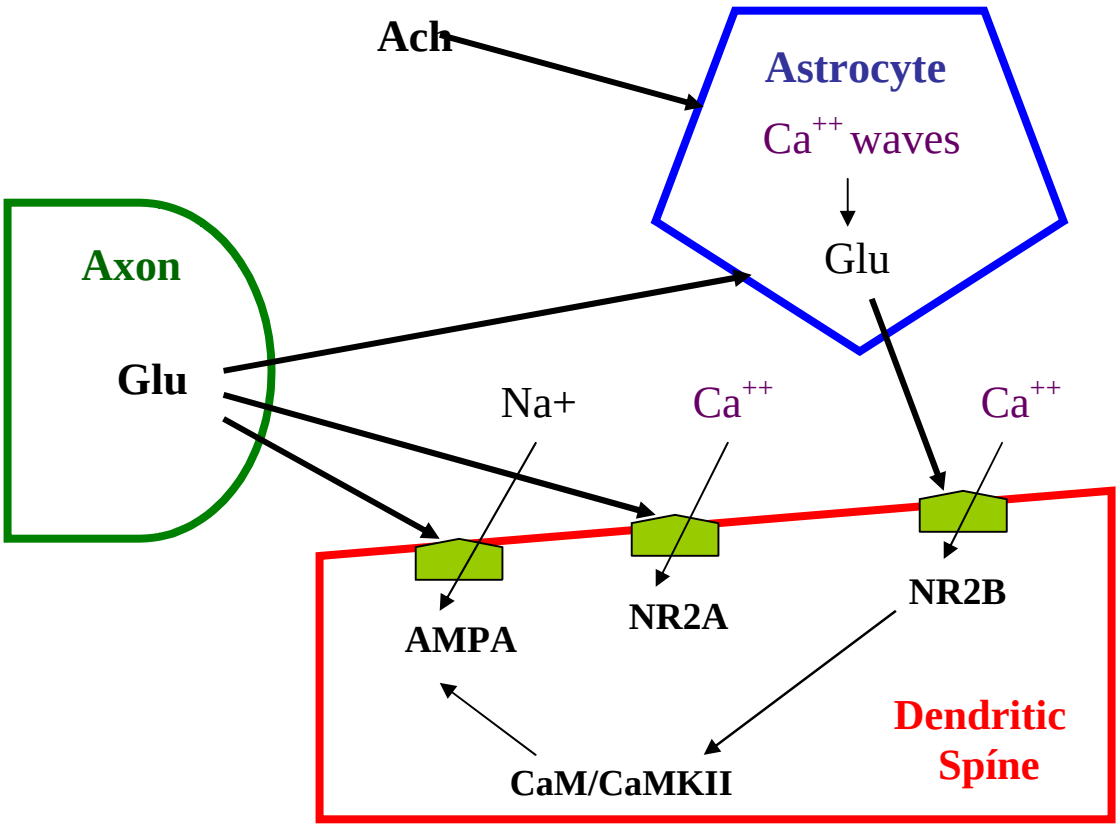

Fig. 1 – Neuro-Astroglial Mechanism Promoting Meta-Potentiation of the Postsynaptic Neuron in a Tripartite Synapse System.

In the awake state, calcium waves in the astrocytic syncytium are previously activated by cholinergic input from neurons, generating high calcium concentrations at the interface with the postsynaptic neuron. In this condition, Glu release from the presynaptic neuron can prompt the release of astroglial glutamate to bind with neuronal NMDA receptors containing the NR2B subunit. The opening of these receptors elicits slow inward currents of calcium ions. The ions enter the cell and bind to calmodulin (CaM) and calmodulin-dependent kinase II (CaMKII) that completes the activating cycle by phosphorylating AMPA. The same action of the astroglial cell on a

neuronal population generates a larger excitatory pattern. By means of this mechanism, the star-shaped astroglial network promotes the coordinated excitation of a large neuronal population, triggering the phenomenon of oscillatory synchrony.

The above model solves a theoretical problem originally identified by Koch (2003, p. 17). The reciprocal activation of neuronal and astroglial NMDA receptors requires the presence of high Ca++ concentrations in the astrocytic terminal that releases Glu to the postsynaptic neuron. How to get high Ca++ concentrations there 150 ms after presynaptic stimulation, considering that Ca++ waves in the astrocytic syncytium are relatively slow (in the scale of seconds)?

One solution is to consider that calcium waves are previously activated during wakefulness. Their readiness for postsynaptic meta-potentiation requires a previous activation of calcium waves in the astrocytic syncytium, regularly made by cholinergic (Seigneur et al., 2006) and other mechanisms (e.g., purinergic; see Di Garbo et al., 2006) during the awake state. One possible signal-transduction pathway involved with cholinergic activation is the increase of extracellular potassium caused by the spiking activity of the postsynaptic neuron, leading to calcium influx to the astrocyte at the site of interaction with the neuron (see Postnov et al., 2007). An implication of the above solution is that during the awakening process the conscious brain would take around 40 seconds to work properly (as discussed by Hobson, 1994).

Slow inward calcium currents through NMDARs can take several seconds to occur, in the case of an exclusive presynaptic Glu activation, but they can become “fast” relatively to the presynaptic excitatory signal, by means of a previous cholinergic activation of calcium waves in astrocytes, raising Ca++ concentrations at the interacting regions. Once Ca++

concentration is high in these regions, the release of astrocytic Glu following a presynaptic activation is relatively “fast” (beginning around 150 ms after the initial phase of the EPSP).

In this condition, calcium currents that flow through NMDARs are able to activate CaM and CaMKII, and then sustain the excitatory pattern elicited in AMPA channels by the external stimulus. Such an extension of the EPSP makes possible for the postsynaptic neuron to participate in a larger neuronal assembly, together with neurons from other brain areas which were sequentially activated by the same stimulation.

5 - Concluding Remarks

In summary, we propose that:

a) meta-potentiation of neuronal populations around tripartite synapses sustains LFPs to participate in a larger collective response;

b) astrocytes are adequate to this task, since these cells, being star-shaped, simultaneously interact with a population of neurons, and

c) astrocytic networks are adequate to coordinate neuronal assemblies, triggering oscillatory synchrony and possibly participating in the process of ‘binding’ informational patterns distributed along the brain.

Each LFP possibly embodies a potential conscious content. In perceptual processes, LFPs that do not sustain activity to participate in the larger collective response possibly do not have their excitatory pattern included in the content of perceptual consciousness. Once the spread of excitation is (meta-)potentiated by astrocytes, other mechanisms contribute to the onset of synchrony and its maintenance: a thalamic pacemaker and electric synapses. An identification of the function of each mechanism may provide a deeper understanding of the mechanisms underlying oscillatory synchrony, the

role of astrocytes in the generation of this phenomenon, and its relation with consciousness.

Acknowledgments: FAPESP, CNPQ (Alfredo P. Jr)

References

Antanitus, D. (1998) A Theory of Cortical Neuron-Astrocyte Interaction. *The Neuroscientist* 4: 154-159.

Buzsaki G (2007) The Structure of Consciousness. *Nature* 446 (7133): 267.

Coull JT (1998) Neural Correlates of Attention and Arousal: Insights from electrophysiology, functional neuroimaging and psychopharmacology. *Progr. Neurobiol*. **55**, 343-361.

Crick F and Koch C (1994) Some Further Ideas Regarding the Neuronal Basis of Awareness. In: Koch C and Davis JL (Eds.) *Large-Scale Neuronal Theories of the Brain.* Cambridge: MIT Press.

Di Garbo A, Barbi M, Chilleni S, Alloisio S and Nobile M (2006) Calcium Signaling in Astrocytes and Modulation of Neural Activity. *BioSystems* 89: 74-83.

Fellin T Pascual O Gobbo S Pozzan T Haydon PG and Carmignoto G (2004) Neuronal Synchrony Mediated by Astrocytic Glutamate Through Activation of Extrasynaptic NMDA Receptors. *Neuron* 43(5): 729-43.

Haydon PG and Carmignoto G (2006) Astrocyte Control of Synaptic Transmission and Neurovascular Coupling. *Physiol Rev.* 86(3): 1009-31.

Hobson JA (1994) *The Chemistry of Conscious States*. Boston: Back Bay Books.

Kamitani Y and Tong F (2005) Decoding the Visual and Subjective Contents of the Human Brain. *Nature Neuroscience* 8(5):679-85

Knight RT (1997) Distributed cortical network for visual attention. *J. Cogn. Neurosci.* 9, 75-91.

Koch, C (2003) *The Quest for Consciousness: a Neurobiological Approach.* Englewood: Roberts and Co.

Laureys S. (2005) The Neural Correlate of (Un)Awareness: Lessons From the Vegetative State. *Trends Cogn Sci.* 9(12): 556-9.

Libet B (1973) Electrical Stimulation of Cortex in Human Subjects and Conscious Sensory Aspects. In: Iggo A. (Ed.) *Handbook of Sensory Physiology*. Berlin: Springer-Verlag.

Libet B (2004) *Mind Time: The Temporal Factor in Consciousness*. Cambridge/London: Harvard University Press.

Lloyd D (2002) Functional MRI and the Study of Human Consciousness. *Journal of Cognitive Neuroscience* 14 (6): 818-831.

Pöppel E (1994) Temporal mechanisms in perception. *International Review of Neurobiology* 37: 185-202.

Pöppel E, Ruhnau E, Schill K, and Steinbuchel NV (1990) A Hypothesis Concerning Time in the Brain. In: *Synergetics of Cognition*, Haken H and Stadler (Eds.), Heidelberg: Springer-Verlag.

Postnov DE, Ryazanova LS and Sosnovtseva OV (2007) Functional Modeling of Neural-Glial Interaction. *BioSystems* 89: 84-91.

Rees G (2007) Neural correlates of the contents of visual awareness in humans. *Philos Trans R Soc Lond B Biol Sci.* 362(1481):877-86.

Rodriguez E, George, N, Lachaux J, Martinerie J, Renault B and Varela FJ (1999) Perception's Shadow: long-distance synchronization of human brain activity. *Nature* 397, p. 430-433.

Seigneur J, Kroeger D, Nita DA and Amzica F (2006) Cholinergic Action on Cortical Glial Cells 'In Vivo'. *Cerebral Cortex* 16: 655-668.